Atty Dkt No. 8500-0262
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The following listing of the claims replaces the claims as filed in the subject application:

LISTING OF THE CLAIMS

1. (Original) A method for increasing the solubility of an ionizable compound in lipophilic medium, wherein ionization of the compound results in a biologically active cationic species in association with an anionic counterion, the method comprising admixing the ionizable compound with an effective solubility enhancing amount of an N,N-dinitramide salt.

2. (Original) The method of claim 1, wherein the ionizable compound is a salt comprised of the biologically active cationic species and an anionic counterion.

3. (Original) The method of claim 2, wherein the biologically cationic species is nitrogen-containing cation containing at least one positively charged nitrogen atom.

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4. (Original) The method of claim 3, wherein the admixing is carried out under conditions that result in replacement of the anionic counterion with N,N-dinitramide anion.

5. (Original) The method of claim 1, wherein the ionizable compound is in electronically neutral form prior to admixture with the N,N-dinitramide salt, but upon admixture with the N,N-dinitramide salt ionizes to form a biologically active cationic species ionically associated with N,N-dinitramide anion.

6. (Original) The method of claim 1, wherein the ionizable compound becomes protonated in an aqueous medium at physiological pH to give a biologically active cationic species in association with hydroxide counterions.

7. (Original) The method of claim 6, wherein the ionizable compound is a nitrogen-containing compound containing at least one nitrogen atom that becomes protonated and thus positively charged in an aqueous medium at physiological pH.

8. (Original) The method of claim 1, wherein the ionizable compound is comprised of a non-ionizable precursor modified so as to contain an ionizable site, wherein ionization of the ionizable site results in the biologically active cationic species.

9. (Original) The method of claim 1, wherein the N,N-dinitramide salt has the formula $M^{+x}[N(NO_2)_2^-]_x$ wherein M is selected so that it is displaced by the biologically active cationic species upon admixture of the N,N-dinitramide salt with the ionizable compound, and x is the cationic charge of M.

10. (Original) The method of claim 1, wherein the N,N-dinitramide salt has the formula $M^{+x}[N(NO_2)_2^-]_x$ wherein M is a cation selected from the group consisting of a metal ion and a nitrogen-containing ion, and x is the cationic charge of M.

11. (Original) The method of claim 10, wherein M is a mono, di, or trivalent metal cation.

12. (Original) The method of claim 11, wherein M is selected from the group consisting of Li, Na, K, Rb, Cs, Ca, Ba, Sr, Mg, Cu, Ag, Au, Zn, Cd, Hg, Al, Sc, Y, Ga, In, lanthanide elements (57-71), Ti, Zr, Hf, Ge, Sn, V, Nb, Ta, Cr, Mo, W, Mn, Tc, Re, Fe, Co, Ni, Ru, Rh, Pd, Os, Ir, and Pt.

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13. (Original) The method of claim 12, wherein M is a metal cation selected from the group consisting of Li, Na, K, Be, and Mg.

14. (Original) The method of claim 10, wherein M is a nitrogen-containing cation.

15. (Original) The method of claim 14, wherein the nitrogen-containing cation is an inorganic nitrogen-containing cation.

16. (Original) The method of claim 15, wherein the inorganic nitrogen-containing cation is selected from the group consisting of ammonium, hydrazinium, nitronium and nitrosonium.

17. (Original) The method of claim 16, wherein the inorganic nitrogen-containing cation is ammonium.

18. (Original) The method of claim 14, wherein the nitrogen-containing cation is an organic nitrogen-containing cation.

19. (Original) The method of claim 18, wherein the organic nitrogen-containing cation is a cationic derivative of an organic compound having one or more tetravalent nitrogen atoms.

20. (Original) The method of claim 19, wherein the organic nitrogen-containing cation contains 1 to 8 carbon atoms.

21. (Original) The method of claim 20, wherein the nitrogen-containing cation contains 1 or 2 carbon atoms.

22. (Original) The method of claim 20, wherein M has the formula $R_kH_mN_n^{+q}$, wherein:
n is an integer in the range of 1 to 8;
k is an integer in the range of 1 to 2 + n;
q is an integer in the range of 1 to n;
m is equal to n + 2 + q - k; and
each R is independent selected from the group consisting of C_1-C_{12} hydrocarbyl moieties.

23. (Original) The method of claim 22, wherein each R is independently selected from the group consisting of linear and branched lower alkyl groups.

24. (Original) The method of claim 23, wherein M is selected from the group consisting of $CH_3NH_3^+$, $(CH_3)_2NH_2^+$, $(CH_3)_3NH^+$, $(CH_3)_4N^+$, $C_2H_5NH_3^+$, $(C_2H_5)_2NH_2^+$, $(C_2H_5)_3NH^+$, $(C_2H_5)_4N^+$, $(C_2H_5)(CH_3)NH_2^+$, $(C_2H_5)(CH_3)_2NH^+$, $(C_2H_5)_2(CH_3)_2N^+$, $(C_3H_7)_4N^+$, $(C_4H_9)_4N^+$, $CH_3N_2H_4^+$, $(CH_3)_2N_2H_3^+$, $(CH_3)_3N_2H_2^+$, $(CH_3)_4N_2H^+$, and $(CH_3)_5N_2^+$.

25. (Currently Amended) The method of claim 18, wherein the organic nitrogen-containing cation is selected from the group consisting of ~~guanidium~~guanidinium, biguanidinium, guanylurea, ethylenediaminium, piperazinediium, monoaminoguanidinium, diaminoguanidinium, triaminoguanidinium, tetrazolium, aminotetrazolium, amino-ammonium-furazan, polyvinylammonium, and dicyandiamidium.

26. (Original) The method of claim 1, wherein the ionizable compound is a pharmacologically active agent, and the biologically active cationic species is a pharmacologically active cationic species.

27. (Original) The method of claim 26, wherein the pharmacologically active agent is selected from the group consisting of: sympathomimetic amines; neuroprotective agents; neuroactive amino acids; neuroactive peptides; neurotransmitters; muscarinic receptor agonists and antagonists; anticholinesterases; neuromuscular blocking agents; ganglionic stimulating drugs; agents to treat neurodegenerative disorders; anti-epileptic agents; CNS and respiratory stimulants; anesthetic agents; analgesic agents; antiemetic agents; antihypertensive agents; cerebral vasodilators; hypnotic agents and sedatives; anxiolytics and tranquilizers; neuroleptic agents; anti-microbial agents; alpha adrenergic receptor antagonists; and appetite suppressants.

28. (Original) The method of claim 27, wherein the pharmacologically active agent is a sympathomimetic amine or a pharmaceutically acceptable acid addition salt thereof.

29. (Currently Amended) The method of claim 28, wherein the sympathomimetic amine is selected from the group consisting of albuterol, amphetamine, benzphetamine, colterol, diethylpropion, dopamine, dobutamine, ephedrine, epinephrine, ethylnorepinephrine, fenfluramine, ~~fenoldapam~~, fenoldopam, hydroxyamphetamine, ibopamine, isoetharine, isoproterenol, mephentermine, metaproterenol, metaraminol, methoxamine, midodrine, norepinephrine, phendimetrazine, phenmetrazine, phentermine, phenylephrine, phenylethylamine, phenylpropanolamine, prenalterol, propylhexedrine, pseudoephedrine, terbutaline, ~~terbutaline sulfate,~~ tyramine, pharmaceutically acceptable acid addition salts thereof, and combinations of any of the foregoing.

30. (Original) The method of claim 27, wherein the pharmacologically active agent is a neuroprotective agent.

31. (Original) The method of claim 30, wherein the neuroprotective agent is a neurotrophic factor.

32. (Original) The method of claim 27, wherein the pharmacologically active agent is a neuroactive amino acid.

33. (Original) The method of claim 27, wherein the pharmacologically active agent is a neuroactive peptide.

34. (Original) The method of claim 27, wherein the pharmacologically active agent is a muscarinic receptor agonist.

35. (Original) The method of claim 27, wherein the pharmacologically active agent is a muscarinic receptor agonist.

36. (Original) The method of claim 27, wherein the pharmacologically active agent is an anticholinesterase.

37. (Original) The method of claim 27, wherein the pharmacologically active agent is a neuromuscular blocking agent.

38. (Original) The method of claim 27, wherein the pharmacologically active agent is a ganglionic blocking drug.

39. (Original) The method of claim 27, wherein the pharmacologically active agent is an agent to treat a neurodegenerative disorder.

40. (Currently Amended) The method of claim 39, wherein the neurodegenerative disorder is Alzheimer's disease and the pharmacologically active agent is selected from the group consisting of ~~donezepil~~ donepezil, physostigmine, tacrine, pharmaceutically acceptable acid addition salts thereof, and combinations of any of the foregoing.

41. (Original) The method of claim 39, wherein the neurodegenerative disorder is Huntington's disease and the pharmacologically active agent is selected from the group consisting of fluoxetine, carbamazepine, and pharmaceutically acceptable acid addition salts and combinations thereof.

42. (Currently Amended) The method of claim 39, wherein the neurodegenerative disorder is Parkinson's disease and the pharmacologically active agent is selected from the group consisting of amantadine, apomorphine, bromocriptine, levodopa, pergolide, ropinirole, selegiline, ~~triexyphenidyl~~ trihexyphenidyl, atropine, scopolamine, glycopyrrolate, pharmaceutically acceptable acid addition salts thereof, and combinations of any of the foregoing.

43. (Original) The method of claim 39, wherein the neurodegenerative disorder is amyotrophic lateral sclerosis (ALS) and the pharmacologically active agent is selected from the group consisting of baclofen, diazepam, tizanidine, dantrolene, pharmaceutically acceptable acid addition salts thereof, and combinations of any of the foregoing.

44. (Original) The method of claim 27, wherein the pharmacologically active agent is an anti-epileptic agent.

45. (Original) The method of claim 27, wherein the pharmacologically active agent is a CNS or respiratory stimulant.

46. (Original) The method of claim 27, wherein the pharmacologically active agent is an analgesic agent.

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47. (Currently Amended) The method of claim 46, wherein the analgesic agent is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, drocode, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propoxyphene, sufentanil, tramadol, apazone, etodolac, ~~difenpiramide~~ diphenpyramide, ~~indomethacine~~ indomethacin, meclofenamate, mefenamic acid, oxaprozin, phenylbutazone, piroxicam, tolmetin, pharmaceutically acceptable acid addition salts thereof, and combinations of any of the foregoing.

48. (Original) The method of claim 27, wherein the pharmacologically active agent is a cerebral vasodilator.

49. (Original) The method of claim 27, wherein the pharmacologically active agent is a neuroleptic agent.

50. (Original) The method of claim 49, wherein the neuroleptic agent is an antidepressant drug selected from the group consisting of tricyclic antidepressants, serotonin reuptake inhibitors and atypical antidepressants.

51. (Original) The method of claim 1, wherein the biologically active cationic species is a metal cation, and the ionizable compound is a metal-based drug, an imaging agent, a diagnostic agent, or a mineral supplement.

52. (Original) The method of claim 51, wherein the ionizable compound is an agriculturally active chemical compound.

53. (Original) The method of claim 52, wherein the agriculturally active chemical compound is a pesticide.

54. (Original) The method of claim 53, wherein the pesticide is selected from the group consisting of acaricides, avicides, bacteriocides, fungicides, insecticides, larvicides, miticides, molluscicides, nematocides, ovicides, predicides, pupicides, and rodenticides.

55. (Original) The method of claim 1, wherein the effective solubility-enhancing amount of an N,N-dinitramide salt is selected to provide a molar ratio of the N,N-dinitramide salt to the ionizable compound in the range of about 0.5z:1 to about 5z:1 wherein z is the charge of the biologically active cationic species.

56. (Original) The method of claim 55, wherein the molar ratio of the N,N-dinitramide salt to the ionizable compound is in the range of about 1z:1 to about 2z:1.

57. (Original) The method of claim 56, wherein the molar ratio of the N,N-dinitramide salt to the ionizable compound is in the range of about 1z:1 to about 1.5z:1.

58. (Original) A salt of N,N-dinitramide anion and a biologically active cation.

59. (Original) The salt of claim 58, wherein the biologically active cation is selected from the group consisting of pharmacologically active cations, positively charged imaging agents, positively charged diagnostic agents, and cationic pesticides.

60. (Original) The salt of claim 59, wherein the biologically active cation is a pharmacologically active cation.

61. (Original) The salt of claim 59, wherein the pharmacologically active cation is selected from the group consisting of protonated pharmacologically active agents, pharmacologically active quaternary ammonium cations, and metal cations.

62. (Original) A pharmaceutical formulation comprising a salt of N,N-dinitramide anion and a pharmacologically active cation in a pharmaceutically acceptable carrier.

63. (Currently amended) The formulation of claim ~~13~~ 62, wherein the pharmacologically active cation is selected from the group consisting of protonated pharmacologically active agents, pharmacologically active quaternary ammonium cations, and metal cations.

64. (Currently amended) The formulation of claim 63, wherein the pharmacologically active cation is present in the pharmaceutical formulation in a therapeutically effective amount that is sufficient to provide a desired pharmacological effect in the central nervous system of a mammalian individual to whom the formulation is administered.

65. (Original) The formulation of claim 64, wherein the therapeutically effective amount is a unit dosage.

66. (Original) The formulation of claim 64, in the form of a tablet.

67. (Original) The formulation of claim 63, wherein the pharmaceutical carrier is a lipophilic liquid, and the formulation is in liquid form.

68. (Original) The formulation of claim 67, wherein the lipophilic liquid is suitable for oral administration.

69. (Original) The formulation of claim 67, wherein the lipophilic liquid is suitable for parenteral administration.

70. (Currently amended) A pharmaceutical formulation comprising (a) ~~a therapeutically effective amount of~~ an ionizable compound that upon ionization gives a pharmacologically active cation, (b) an effective solubility enhancing amount of an N,N-dinitramide salt, and (c) a pharmaceutically

acce ble carrier, wherein the ionizable compound is present in an a unt that, when the compound is ioniz , results in a therapeutically effective amount of the pharmaco ically active cation to provide a desir pharmacological effect in the central nervous system of a ma alian individual to whom the form ation is administered.

71. (Original) The formulation of claim 70, wherein the pha acologically active cation is selec d from the group consisting of protonated pharmacologically a ve agents, pharmacologically activ quaternary ammonium cations, and metal cations.

72. (Canceled)

73. (Currently amended) The formulation of claim ~~72~~ 70, w rein the therapeutically effective amo t is a unit dosage.

74. (Currently amended) The formulation of claim ~~72~~ 70, in the form of a tablet.

75. (Original) The formulation of claim 70, wherein the ph maceutical carrier is a lipophilic liqu , and the formulation is in liquid form.

76. (Original) The formulation of claim 75, wherein the lip hilic liquid is suitable for oral adn istration.

77. (Original) The formulation of claim 75, wherein the lip hilic liquid is suitable for par teral administration.

78. (Original) A biologically active agent delivery system mprised of:

(a) an N,N-dinitramide salt having the formula $M^{+x}[N(NO_2)_2]_x$ wherein M is a cation selected fro the group consisting of a metal ion and a nitrogen-containing , and x is the cationic charge of M; an

(b) an ionizable compound, wherein ionization of the comp nd results in a pharmacologically act e cation.

79. (Original) The delivery system of claim 78, wherein the N,N-dinitrami salt and the ionizable compound are physically segregated.

80. (Original) The delivery system of claim 78, wherein the N,N-dinitrami salt and the ionizable compound are contained within a single composition.

81. (Currently amended) A method of transmitting a pharmacologically ac e agent across the blood-brain barrier in a mammalian individual to achieve a desired pharmacologica ffect in the central nervous system, comprising:

administering a therapeutically effective amount of the active agent to pro le the desired pharmacological effect and an effective solubility enhancing amount of an N,N-din amide salt to the individual in a manner that allows the active agent to enter the bloodstream, where the active agent is an ionizable compound that upon ionization results in a pharmacologically active cati